Applicant is in the process of preparing a Declaration to substantiate the unexpected effect of ethanol in enhancing the stability of ranitidine in aqueous oral formulations. However, Applicant does not believe that the Declaration will be available for filing at the Patent Office for another six weeks. Applicant is making every effort to expedite preparation of the Declaration; however, due to circumstances beyond the control of the Applicant, there have been unexpected delays in obtaining the executed Declaration.

Applicant at this time wishes to direct the attention of the Examiner to additional information which may be material to the prosecution of the present application. This information is listed on attached form PTO-1449 and copy of each will be submitted to the Examiner as soon as copies are available.

Both of the listed publications were cited in connection with the corresonding applications in France and Belgium. FR-A-2,547,727 is another equivalent to GB-A-2,142,820 (of record).

French application 2,501,206 relates to novel compounds which are structurally different from ranitidine. Inasmuch as it discloses pharmaceutical formulations, this reference refers only to prior art formulation techniques and applies these to the novel compounds which are disclosed. There is no teaching in this reference whatever that the stability of ranitidine in aqueous solution (or indeed the stability of the novel compounds with which the reference is concerned) can be enhanced by the addition of ethanol.

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In view of the above comments and amendments to the claims, favorable reconsideration and allowance of all claims now present in the application are believed to be in order and are most respectfully requested.

Respectfully submitted,

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Date: October 31, 1990

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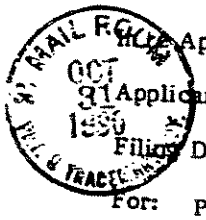
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Application Serial No.: 07/494,804

Applicant: David R. LONG

Filing Date: 03/14/90

Group Art Unit: 125

Examiner: FRIEDMAN

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

☐ one month ☒ three months
☐ two months ☐ four months

The fee set in 37 CFR 1.17 for the extension of time is $ 430.00 .

☒ Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200 . A duplicate copy of this paper is enclosed.

☐ Charge fee to Deposit Account No. _____. A duplicate copy of this paper is enclosed.

☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

☐ has been filed ☐ is enclosed

Also enclosed is a:

☐ Response ☐ Notice of Appeal ☐ Appeal Brief

☐ _____

Respectfully submitted,

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REF/er

Date: October 31, 1990

X The certified copy has been filed in prior application Serial No. 07/131,442 filed Dec. 11, 1987.

X The prior application is assigned of record to GLAXO GROUP LIMITED

X Also enclosed Petition for one month extension of time w/$62

X The power of attorney appears in the original papers in the prior application, and the power of attorney in the prior application includes:
Richard E. Fichter, Reg. No. 26,382 of Bacon & Thomas

It is understood that secrecy under 35 U.S.C. 122 is hereby waived to the extent that if information or access is available to any one of the applications in the file wrapper of a 37 C.F.R. 1.62 application, be it either this application or a prior application in the same file wrapper, the Patent and Trademark Office may provide similar information or access to all the other applications in the same file wrapper.

X Address all future communications to:

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Date: March 14, 1990

#12
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11/21/91

Sheet 1 of 1

FORM PTO–1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
REF/Long/804	07/494,804
APPLICANT: David R. LONG	
FILING DATE: 03/14/90	GROUP: 125

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
DG		FR-A-2,547,727	12/84	France	~~NONE~~	31/54	—	—
DG		GB-A-2,142,820	1/85	Great Britain	~~NONE~~	31/54	—	—

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER: Julie Chrobner

DATE CONSIDERED: 1-17-91

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(19) RÉPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
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(12) DEMANDE DE BREVET D'INVENTION A1

(22) Date de dépôt : 11 mai 1984.

(30) Priorité : GB. 13 mai 1983, n° 83 13217.

(43) Date de la mise à disposition du public de la demande : BOPI « Brevets » n° 52 du 28 décembre 1984.

(60) Références à d'autres documents nationaux apparentés :

(71) Demandeur(s) : *GLAXO GROUP LIMITED.* — GB.

(72) Inventeur(s) : John Malcolm Padfield et Iain Keith Winterborn.

(73) Titulaire(s) :

(74) Mandataire(s) : Regimbeau, Corre, Martin, Schrimpf, Warcoin et Ahner.

(54) Compositions pharmaceutiques.

(57) L'invention a pour objet des compositions aqueuses de ranitidine et/ou d'un ou plusieurs de ses sels physiologiquement acceptables.

On constate que la durée de conservation est nettement prolongée lorsqu'on règle le pH de la composition entre 6,5 et 7,5.

Compositions aqueuses appropriées pour injections, par administration intraveineuse ou intramusculaire, par perfusions continues ou par voie orale sous forme d'un sirop, dans le cadre d'un traitement anti-histaminique.

FR 2 547 727 - A1

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La présente invention concerne une composition pharmaceutique contenant, à titre d'ingrédient actif, une ranitidine antagoniste à l'histamine H_2.

La ranitidine (N-[2-[[5-(diméthylamino) méthyl-2-furanyl]méthyl]thio]éthyl]-N'-méthyl-2-nitro-1,1-éthène-diamine) et ses sels physiologiquement acceptables sont décrits dans le brevet GB 1.565.966. Dans ce brevet il est question de compositions liquides pour administration par voie orale ou parentérale et on donne une description d'une composition à base aqueuse pour administration par voie intraveineuse et d'une autre pour un sirop à usage oral. Ces deux compositions contiennent suffisamment d'acide chlorhydrique pour avoir un pH de 5,0. En outre, les compositions injectables sont décrites par Padfield et al (The Chemical Use of Ranitidine, Medicine Publishing Foundation Symposium Series 5, Oxford : Medicine Publishing Formulation 1982 pp 18-22) sous forme d'une simple solution aqueuse de chlorhydrate de ranitidine et à son pH naturel, c'est-à-dire d'environ 5,5. Alors que de telles compositions contenant la ranitidine et/ou ses sels physiologiquement acceptables sont thérapeutiquement efficaces, elles présentent l'inconvénient d'une durée de conservation relativement brève par suite de la rupture de la ranitidine.

La Demanderesse a maintenant trouvé de façon surprenante qu'on peut prolonger notablement la durée de conservation des compositions à base aqueuse contenant la ranitidine et/ou un ou plusieurs de ses sels physiologiquement acceptables si on règle le pH de la composition entre 6,5 et 7,5.

Ainsi, la présente invention fournit une composition pharmaceutique qui est une composition aqueuse de la ranitidine et/ou d'un ou plusieurs de ses sels physiologiquement acceptables, ayant un

pH de 6,5 à 7,5. On prépare la composition aqueuse en utilisant des ingrédients d'une pureté telle que la composition soit à l'état permettant son administration à des patients.

Les compositions de ranitidine à base aqueuse selon l'invention sont particulièrement stables par comparaison avec des compositions d'un plus faible pH. Ainsi par exemple, dans le cas d'une solution injectable de chlorhydrate de ranitidine (25mg/ml) tamponnée au pH approprié avec des phosphates et soumise à une conservation à 20°C, la rupture de la ranitidine est d'environ 10 fois plus rapide quand la solution est tamponnée à pH 5,5 que lorsque la solution est tamponnée à pH 7,0.

Commodément, on règle le pH de la composition selon l'invention au stade de sa fabrication dans l'intervalle de 6,5 à 7,5 en utilisant pour cela des sels-tampons convenables, par exemple le dihydrogéno-o-phosphate potassique et l'hydrogèno-o-phosphate disodique ou l'acide citrique et l'hydrogéno-o-phosphate disodique.

Les compositions préférées selon l'invention sont celles dont le pH est de 6,7 à 7,3, par exemple de 6,8 à 7,1.

Un mode de réalisation préféré de l'invention est une composition aqueuse pour administration parentérale. Une telle composition peut comprendre de l'eau pour injections dans laquelle on a dissous la ranitidine et/ou un ou plusieurs de ses sels physiologiquement acceptables et des sels appropriés de tamponnement. De préférence, on règle la solution à tonicité par l'addition d'excipients classiques appropriés, par exemple de

chlorure de sodium. Facultativement, la composition peut aussi contenir un agent de préservation antimicrobien tel que le phénol.

La concentration de ranitidine dans des compositions injectables, par exemple par voie intraveineuse ou intramusculaire, est comprise normalement entre 10 et 100 mg/ml et est, par exemple, de l'ordre de 25 mg/ml, exprimée en base libre. Eventuellement on peut diluer la solution avant emploi avec, par exemple, une solution saline isotonique ou une solution de dextrose. Les solutions convenant pour une perfusion lente continue peuvent présenter une concentration de ranitidine de 0,1 à 2,0 mg/ml de préférence de 0,5 à 1,0 mg/ml, exprimée en base libre. Les solutions pour perfusion continue lente peuvent être présentées sous cette forme, par exemple en flacons de 50 à 100 ml ou elles peuvent être présentées sous une forme plus concentrée, c'est-à-dire de 10 à 100 mg/ml, par exemple 25 mg/ml, en vue d'une dilution ultérieure avant utilisation, par exemple avec une solution saline isotonique ou une solution de dextrose.

On prépare commodément les compositions aqueuses pour administration parentérale en dissolvant la ranitidine et/ou un ou plusieurs de ses sels physiologiquement acceptables et des excipients dans une eau appropriée pour injection. La solution dans laquelle on a commodément diffusé un gaz inerte tel que l'azote, est stérilisée, de préférence par filtration et ensuite conditionnée sur un mode aseptique dans des récipients convenables tels que des ampoules, des fioles ou des récipients pour perfusion, sous une atmosphère d'azote. En variante, on peut stériliser la composition en fin de traitement, par exemple par chauffage.

Un autre mode de réalisation préféré de l'invention est une composition aqueuse pour administration

orale. Une telle composition peut comprendre la ranitidine et/ou un ou plusieurs de ses sels physiologiquement acceptables dissous dans l'eau, ensemble avec des sels tampons, un agent de conservation et un agent de rehaussement de la viscosité. Facultativement, la composition peut contenir d'autres excipients classiques tels qu'un édulcorant, un agent de saveur et/ou des adjuvants d'aromatisation.

Parmi les sels-tampons convenables pour des compositions orales on peut citer le dihydrogéno-o-phosphate de potassium et l'hydrogéno-o-phosphate disodique ou l'acide citrique et l'hydrogéno-o-phosphate disodique.

Comme exemples d'agents de rehaussement de la viscosité, on peut citer la gomme de xanthane, le sorbitol, le glycérol, le saccharose ou un dérivé cellulosique tel que la carboxyméthylcellulose ou un éther de cette dernière tel qu'un éther alkylique et/ou hydroxyalkylique de cellulose comme, par exemple, l'hydroxypropylcellulose.

Comme agents de conservation appropriés, on peut citer les hydroxybenzoates d'alkyle tels que les hydroxybenzoates de méthyle, éthyle, propyle et/ou butyle.

Les édulcorants convenables sont la saccharine sodique, le cyclamate de sodium, le sorbitol et le saccharose.

La concentration de ranitidine dans la composition orale exprimée en base libre est commodément de 20 à 400 mg par 10 ml, par exemple de 20 à 200 mg par 10 ml et plus particulièrement 150 mg par dose de 10 ml.

On prépare commodément les compositions aqueuses pour administration par voie orale en ajoutant une solution aqueuse de ranitidine et/ou d'un ou plusieurs de ses sels ensemble avec les autres excipients à une

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solution ou dispersion aqueuse de l'agent de rehaussement de la viscosité.

Les compositions aqueuses selon l'invention sont préparées, de préférence, avec la ranitidine sous forme de son chlorhydrate.

Les exemples suivants servent à illustrer l'invention sans aucunement en limiter la portée. Dans ces exemples les proportions relatives de chlorhydrate de ranitidine et de sels-tampons sont telles que le pH de la composition soit d'environ 7.

Injection de ranitidine pour administration intraveineuse (25 mg/ml)

EXEMPLE 1

	mg/ml
Chlorhydrate de ranitidine	28
Dihydrogéno-o-phosphate de potassium	0,96
Hydrogéno-o-phosphate disodique anhydre	2,4
Phénol Codex	5
Eau q.s.p 1 ml pour injection Codex	

On dissout dans l'eau d'injection le chlorhydrate de ranitidine, les sels-tampons et le phénol. On diffuse de l'azote dans la solution, on stérilise par filtration et ensuite on conditionne de façon aseptique dans des fioles sous atmosphère d'azote et on ferme hermétiquement à l'aide d'un dispositif de fermeture convenable.

EXEMPLE 2

	mg/ml
Chlorhydrate de ranitidine	28
Dihydrogéno-o-phosphate de potassium	0,96
Hydrogéno-o-phosphate disodique anhydre	2,4
Chlorure de sodium Codex	1,6
Eau q.s.p 1 ml pour injection Codex	

On prépare une solution aqueuse de chlorhydrate de ranitidine, de sels tampons et de chlorure de sodium en utilisant l'eau pour injection. On diffuse dans la solution de l'azote, on stérilise par filtration et on conditionne de façon aseptique dans des ampoules sous

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atmosphère d'azote.

Composition liquide de ranitidine pour administration par voie orale (150 mg/10 ml

EXEMPLE 3

	%pds/vol.
Chlorhydrate de ranitidine	1,68
hydroxypropyl méthylcellulose	q.s
parabènes (agents de conservation)	q.s
dihydrogéno-o-phosphate de potassium	0,095
hydrogéno-o-phosphate disodique anhydre	0,350
agent (s) édulcorant(s)	q.s
agent de saveur	q.s

eau purifiée Codex q.s.p 100 ml

On ajoute avec mélange une solution de chlorhydrate de ranitidine ensemble avec les autres excipients à l'exception de l'hydroxypropylméthylcellulose, dans l'eau purifiée à une dispersion de l'hydroxypropylméthylcellulose dans l'eau purifiée.

Compositions de ranitidine pour perfusion intraveineuse lente

	Exemple 4 Pour une perfusion de 50 ml mg/ml	Exemple 5 Pour une perfusion de 100 ml mg/ml
Chlorhydrate de ranitidine	1,12	0,56
Acide citrique Codex	0,3	0,3
Hydrogéno-o-phosphate disodique anhydre	1,8	1,8
Chlorure de sodium Codex	4,5	4,5
Eau pour injections Codex	q.s.p 50,0 ml	q.s.p 100,0 ml

On prépare une solution aqueuse du chlorhydrate de ranitidine, des sels-tampons et du chlorure de sodium en utilisant l'eau pour injections. On diffuse de l'azote dans la solution, on remplit des récipients appropriés pour administrer la solution par perfusion intraveineuse lente, et on stérilise en autoclave.

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REVENDICATIONS

1.- Composition pharmaceutique, caractérisée en ce qu'elle est une composition aqueuse de ranitidine et/ou d'un ou plusieurs de ses sels physiologiquement acceptables, le pH de la composition étant compris entre 6,5 et 7,5.

2.- Composition selon la revendication 1, caractérisée en ce que son pH est de 6,7 à 7,3.

3.- Composition selon la revendication 1, caractérisée en ce que son pH est de 6,8 à 7,1.

4.- Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce que le pH est réglé au moyen de sels-tampons appropriés.

5.- Composition selon la revendication 4, caractérisée en ce que les sels tampons sont le dihydrogéno-o-phosphate de potassium et l'hydrogéno-o-phosphate disodique ou l'acide citrique et l'hydrogéno-o-phosphate disodique.

6.- Composition selon l'une quelconque des revendications 1 à 5,caractérisée en ce qu'elle est appropriée pour une administration parentérale.

7.- Composition selon la revendication 6, caractérisée en ce qu'elle est appropriée pour des injections et contient de 10 à100 mg/ml de ranitidine, exprimée en base libre.

8.- Composition selon la revendication 6, caractérisée en ce qu'elle est sous une forme appropriée pour perfusion lente continue et contient 0,1 à 2,0 mg/ml de ranitidine, exprimée en base libre.

9.- Composition selon l'une quelconque des revendications 1 à 5, caractérisée en ce qu'elle est sous une forme appropriée pour administration par voie orale.

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10.- Composition selon la revendication 9, caractérisée en ce qu'elle contient de 20 à 400 mg de ranitidine par dose de 10 ml.

11.- Composition selon l'une quelconque des revendications 1 à 10, caractérisée en ce qu'elle contient de la ranitidine sous forme de son chlorhydrate.

12.- Procédé de production d'une composition pharmaceutique selon l'une quelconque des revendications 1 à 11, caractérisé en ce qu'on traite les divers composants pour obtenir une composition aqueuse pouvant être administrée aux patients.

13.- Procédé selon la revendication 12 servant à la production d'une composition pour administration parentérale, caractérisé en ce qu'on dissout la ranitidine et/ou un ou plusieurs de ses sels physiologiquement acceptables et les composants restants dans l'eau appropriée pour injection, puis on stérilise.

14.- Procédé selon la revendication 12 pour la production d'une composition pour administration par voie orale, caractérisé en ce qu'on ajoute une solution aqueuse de ranitidine et/ou un ou plusieurs de ses sels physiologiquement acceptables à une solution ou dispersion aqueuse d'un agent d'amélioration de la viscosité.

(12) UK Patent Application (19) GB (11) 2 142 820 A

(43) Application published 30 Jan 1985

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None

(58) Field of search
A5B

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(54) Aqueous compositions of ranitidine

(57) Aqueous formulations of raniditine have been found to have enhanced shelf life provided that they are formulated with a pH in the range 6.5–7.5. Suitable aqueous formulations include injections for intravenous and intramuscular administration, continuous infusions and oral preparations such as syrups.

GB 2 142 820 A

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SPECIFICATION

Pharmaceutical compositions

The present invention relates to a pharmaceutical composition containing as active ingredient the histamine H_2 antagonist ranitidine.

Ranitidine [N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethene-diamine] and its physiologically acceptable salts are described in British Patent Specification No. 1565966. In that specification there is reference to liquid formulations for oral and parenteral administrations and there is a description of an aqueous based formulation for intravenous administration and another of an oral syrup. Both of these formulations contain sufficient hydrochloric acid to achieve a pH of 5.0. In addition injection formulations are described by Padfield et al (The Chemical Use of Ranitidine, Medicine Publishing Foundation Symposium Series 5, Oxford:Medicine Publishing Formulation 1982 pp 18–22) in the form of a simple aqueous solution of ranitidine hydrochloride at is natural pH, i.e. about 5.5. Whilst such formulations containing ranitidine and/or its physiologically acceptable salts are therapeutically effective they suffer from the disadvantage of having a relatively short shelf life due to the breakdown of the ranitidine.

We have now surprisingly found that the shelf life of aqueous based formulations containing ranitidine and/or one or more of its physiologically acceptable salts may be significantly enhanced if the pH of the formulation is adjusted within the range of 6.5–7.5.

Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salt thereof, having a pH within the range of 6.5–7.5. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients.

The aqueous based ranitidine formulations according to the invention are particularly stable when compared with formulations at a lower pH. Thus for example, in the case of a 25 mg/ml ranitidine hydrochloride injection solution buffered to the appropriate pH with phosphate salts and subjected to storage at 20°C, the rate of breakdown of the ranitidine is about ten times faster for a solution buffered to pH 5.5 than for a solution buffered to pH 7.0.

Conveniently the pH of the formulation according to the invention is adjusted on manufacture within the range 6.5–7.5 by means of the use of suitable buffer salts, for example, potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

Preferred formulations according to the invention are those wherein the pH is within the range 6.7 to 7.3, for example 6.8 to 7.1.

A preferred embodiment of the invention is an aqueous formulation for parenteral administration. Such a formulation may comprise water suitable for injections in which is dissolved ranitidine and/or one or more of its physiologically acceptable salts and suitable buffer salts. Preferably the solution is adjusted to tonicity by the addition of the appropriate conventional excipients e.g. sodium chloride. Optionally the composition may also contain an antimicrobial preservative, for example phenol.

The concentration of ranitidine in formulations suitable for injection, e.g. intravenous or intramuscular injection is conveniently within the range 10–100 mg/ml, for example 25 mg/ml, expressed as free base. If desired, the solution may be diluted prior to use with, for example, an isotonic saline solution or a dextrose solution. Solutions suitable for continuous infusion may have a concentration of ranitidine of 0.1–2.0 mg/ml, preferably 0.5–1.0 mg/ml, expressed as free base. The solutions for continuous infusion may be presented in this form, for example in packs of 50–100 ml, or may be presented in a more concentrated form, i.e. 10–100 mg/ml, e.g. 25 mg/ml, for subsequent dilution before use, with, for example, an isotonic saline solution or a dextrose solution.

The aqueous formulations for parenteral administration are conveniently prepared by dissolving ranitidine and/or one or more of its physiologically acceptable salts and the excipients in water suitable for injections. The solution, which conveniently is sparged with an inert gas such as nitrogen, is sterilised preferably by filtration and then aseptically packed into suitable containers, e.g. ampoules, vials or containers for infusion, under an atmosphere of nitrogen. Alternatively the formulation may be terminally sterilized, for example by heating.

A further preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, together with buffer salts, a preservative and a viscosity enhancing agent. Optionally the composition may also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids.

Suitable buffer salts for the oral formulation include potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

Examples of suitable viscosity enhancing agents include Xanthan gum, sorbitol, glycerol,

sucrose or a cellulose derivative such as carboxymethyl cellulose or an ether thereof such as an alkyl and/or a hydroxyalkyl ether of cellulose as for example hydroxypropyl methyl-cellulose.

Suitable preservatives include the alkyl hydroxybenzoates, such as methyl, ethyl, propyl and/or butyl hydroxybenzoates.

Suitable sweeteners include saccharin sodium, sodium cyclamate, sorbitol and sucrose.

The concentration of ranitidine in the oral formulation, expressed as free base is conveniently within the range of 20–400 mg per 10 ml, for example 20–200 mg per 10 ml, more particularly 150 mg per 10 ml dose.

The aqueous formulations for oral administration are conveniently prepared by adding an aqueous solution of ranitidine and/or one or more of its salts together with the other excipients to an aqueous solution or dispersion of the viscosity enhancing agent.

The aqueous formulations according to the invention are preferably prepared using ranitidine in the form of its hydrochloride salt.

Illustrative examples of formulations according to the invention are as follows. In these examples the relative proportions of ranitidine hydrochloride and buffer salts are such that each formulation has a pH of approximately 7.

Raniditine Injection for Intravenous administration (25 mg/ml)

Example 1

	mg/ml
Ranitidine hydrochloride	28
Potassium dihydrogen orthophosphate	0.96
Disodium hydrogen orthophosphate, anhydrous	2.4
Phenol BP	5
Water Suitable for Injections BP to	1 ml

Ranitidine hydrochloride, the buffer salts and the phenol were dissolved in Water for Injection. The solution was sparged with nitrogen, sterilised by filtration and then aseptically packed into vials under an atmosphere of nitrogen and sealed with a suitable closure.

Example 2

	mg/ml
Ranitidine hydrochloride	28
Potassium dihydrogen orthophosphate	0.96
Disodium hydrogen orthophosphate, anhydrous	2.4
Sodium chloride BP	1.6
Water Suitable for Injections BP to	1 ml

An aqueous solution of the ranitidine hydrochloride, the buffer salts and sodium chloride was prepared using Water for Injection. The solution was sparged with nitrogen, sterilised by filtration and then aseptically packed into ampoules under an atmosphere of nitrogen.

Ranitidine oral liquid formulation (150 mg/10 ml)

Example 3

	% w/v
Ranitidine hydrochloride	1.68
Hydroxypropyl methylcellulose	q.s.
Parabens (preservative)	q.s.
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate, anhydrous	0.350
Sweetening agent(s)	q.s.
Flavour	q.s.
Purified Water BP to	100 ml

A solution of the ranitidine hydrochloride together with the other excipients, except hydroxypropyl methylcellulose, in purified water was added with mixing to a dispersion of the hydroxypropyl methylcellulose in purified water.

Ranitidine formulations for intravenous infusion.

	Example 4 For a 50 ml Infusion mg/ml	Example 5 For a 100 ml Infusion mg/ml
Ranitidine hydrochloride	1.12	0.56
Citric acid BP	0.3	0.3
Disodium hydrogen orthophosphate, anhydrous	1.8	1.8
Sodium chloride BP	4.5	4.5
Water Suitable for Injections BP	to 50.0 ml	to 100.0 ml

An aqueous solution of the ranitidine hydrochloride, the buffer salts and the sodium chloride is prepared using Water for Injections. The solution is sparged with nitrogen, filled into containers suitable for administering the solution by intravenous infusion, and sterilised by autoclaving.

CLAIMS

1. A pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof, the formulation having a pH within the range 6.5–7.5.
2. A pharmaceutical composition as claimed in claim 1 having a pH in the range 6.7 to 7.3.
3. A pharmaceutical composition as claimed in claim 1 having a pH in the range 6.8 to 7.1.
4. A pharmaceutical composition as claimed in any of claims 1 to 3 in which the pH is adjusted by means of suitable buffer salts.
5. A pharmaceutical composition as claimed in claim 4 in which the buffer salts are potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.
6. A pharmaceutical composition as claimed in any of claims 1 to 5 in a form suitable for parenteral administration.
7. A pharmaceutical composition as claimed in claim 6 in a form suitable for injection and containing 10 to 100 mg/ml ranitidine, expressed as free base.
8. A pharmaceutical composition as claimed in claim 6 in a form suitable for continuous infusion and containing 0.1–2.0 mg/ml ranitidine, expressed as free base.

9. A pharmaceutical composition as claimed in any of claims 1 to 5 in a form suitable for oral administration.

10. A pharmaceutical composition as claimed in claim 9 containing 20–400 mg per 10 ml dose.

11. A pharmaceutical composition as claimed in any of claims 1 to 10, containing ranitidine in the form of its hydrochloride salt.

12. A process for the production of a pharmaceutical composition as claimed in any of claims 1 to 11 which comprises processing the various components to provide an aqueous formulation suitable for administration to patients.

13. A process as claimed in claim 12 for the production of a composition suitable for parenteral administration, which comprises dissolving ranitidine and/or one or more physiologically acceptable salts thereof and the remaining constituents in water suitable for injection, followed by sterilisation.

14. A process as claimed in claim 12 for the production of a composition suitable for oral administration which comprises adding an aqueous solution of ranitidine and/or one or more physiologically acceptable salts thereof to an aqueous solution or dispersion of a viscosity enhancing agent.

Printed in the United Kingdom for Her Majesty's Stationery Office. Dd 8818935. 1985. 4235.
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

pt. 1-15-91

#13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
David R. LONG	:	Examiner: FRIEDMAN
Serial No.: 07/494,804	:	Group Art Unit: ~~125~~ 12-X
Filed: March 14, 1990	:	
For: PHARMACEUTICAL COMPOSITIONS	:	Gardner

LETTER OF TRANSMITTAL

RECEIVED
91 JAN 10 PM 2:23
GROUP 120

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

SIR:

Applicants submit herewith a copy of the documents referred to in the Amendment filed October 31, 1990 and which are identified on the Form PTO-1449 attached to the October 31, 1990 Amendment.

Reconsideration and allowance of all the claims now present in the application in view of the Amendment filed October 31, 1990 is most respectfully requested.

Respectfully submitted,

Richard E. Fichter

Richard E. Fichter
Registration No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
Telephone: (703) 683-0500

REF/er

Date: January 9, 1991

90

Sheet 1 of 1

FORM PTO-1449 (Rev. 2-32) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
REF/Long/804	07/494,804
APPLICANT: David R. LONG	
FILING DATE: 03/14/90	GROUP: 125

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
DG		FR-A-2,547,727	12/84	France	A61K	31/34	—	—
DG		GB-A-2,142,820	1/85	Great Britain	A61K	31/34	—	—

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER	DATE CONSIDERED
Dennis Gardner	Jan. 17, 1991

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

91

Law

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/494,804 03/14/90 LONG D

GARDNER, D

RICHARD E. FICHTER
BACON & THOMAS
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314

125 14

01/22/91

☒ This application has been examined ☒ Responsive to communication filed on 1-10-91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-3, 5-7, 12-17 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 5-7, 12-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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PTOL-326 (Rev.5-88) EXAMINER'S ACTION

The following Office Action is a result of the telephone conversation conducted between Richard Fichter and myself on 1/17/91. Claims 1-3, 5-7 and 12-17 are pending at this time.

Rejections presented by Examiner Friedman in the Office Action dated 5/4/90 are deemed to be overcome by the amendment filed on 10/31/90.

However, new rejections must now be presented as a result of the additional documents which were filed on 1/10/91.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country,

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or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-7 and 12-17 are rejected under 35 U.S.C. § 102(a) and (b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Padfield et al. (GB 2142820). Padfield et al. teach the enhanced stability of aqueous compositions of ranitidine formulated at a pH in the range of 6.5 to 7.5. The applicant's invention is directed to aqueous compositions of ranitidine formulated at a pH in the rage of 6.5 to 7.5 and with the addition of ethanol. It has not been demonstrated in the record, by means of experimental data, that the applicant's invention produces any unexpected results. The disclosure, as presented, is insufficient to overcome the prior art without the aid of experimental data to show a definite improvement over the GB patent. Since the GB patent teaches an aqueous composition of ranitidine, it is considered well within the state of the art to choose ethanol as an additive which would be considered pharmaceutically acceptable when formulating this composition. Absent evidence to the contrary, the addition of ethanol is considered merely to be a choice among known conventional excipients.

No claims area allowed.

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It is noted that the amendment dated 10/31/90 stated that a new Declaration was in the process of being prepared. This paper has not yet been received.

Any inquiry concerning this communication should be directed to Diane Gardner at telephone number (703) 308-3727.

FREDERICK E. WADDELL
EXAMINER
GROUP ART UNIT 125

Diane Gardner
January 17, 1990

85

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Serial No.: 07/494,804

Applicant: David R. LONG

Group Art Unit: 125

Filing Date: March 14, 1990

Examiner: GARDNER

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

☒ one month ☐ three months
☐ two months ☐ four months

The fee set in 37 CFR 1.17 for the extension of time is $ 100.00.

☒ Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200. A duplicate copy of this paper is enclosed.

☐ Charge fee to Deposit Account No. _____. A duplicate copy of this paper is enclosed.

☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

☐ has been filed ☐ is enclosed

Also enclosed is a:

☐ Response ☐ Notice of Appeal ☐ Appeal Brief

☒ Request for Reconsideration
Declaration of John Hempenstall

Respectfully submitted,

Richard E. Fichter
Reg. No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500
REF/er

Date: May 10, 1991

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application Serial No.: 07/494,804

Applicant: David R. LONG

Group Art Unit: 125

Filing Date: March 14, 1990

Examiner: GARDNER

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

☒ one month ☐ three months
☐ two months ☐ four months

The fee set in 37 CFR 1.17 for the extension of time is $ 100.00.

☒ Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200. A duplicate copy of this paper is enclosed.

☐ Charge fee to Deposit Account No. _____. A duplicate copy of this paper is enclosed.

☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

☐ has been filed ☐ is enclosed

Also enclosed is a:

☐ Response ☐ Notice of Appeal ☐ Appeal Brief

☒ Request for Reconsideration
Declaration of John Hempenstall

Respectfully submitted,

Richard E. Fichter
Reg. No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500
REF/er

Date: May 10, 1991

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
David R. LONG	:	Examiner: Gardner
Serial No.: 07/494,804	:	Group Art Unit: 125
Filed: March 14, 1990	:	
For: PHARMACEUTICAL COMPOSITIONS	:	

REQUEST FOR RECONSIDERATION

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

This is in response to the Official Action dated January 22, 1991, the period for response to which has been extended to expire on May 22, 1991, by the filing herewith of a petition for a one month extension of time and payment of the required fee.

The outstanding Official Action sets forth a rejection of all of the claims under 35 U.S.C. §102(a) and (b) as anticipated by, or, in the alternative, under 35 U.S.C. §103 as obvious over Padfield et al. (Great Britain 2142820). The Official Action maintains that the Padfield et al. publication teaches the enhanced stability of aqueous compositions of ranitidine formulated at a pH in the range of 6.5 to 7.5. Applicant's invention is directed to aqueous compositions of ranitidine formulated at a pH in the range of 6.5 to 7.5 with the addition of ethanol.

The Official Action urges that it has not been demonstrated in the record by means of experimental data that Applicant's invention produces any unexpected results. In addition, it is stated that, absent evidence to the contrary, the addition of

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ethanol is considered merely to be a choice among known conventional excipients. These rejections, having been carefully considered, are most respectfully traversed.

Applicant submits herewith a Declaration of Dr. John Hempenstall which provides convincing evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-2142820 in terms of the stability of the ranitidine in the composition. In this connection, it is noted that the liquid formulation without ethanol which is used in the Declaration for purposes of comparison is the same as the formulation of Example 3 of Padfield et al. Accordingly, the Declaration presents a direct comparison between a composition according to the present invention and a composition according to the prior art.

The Official Action bases the rejection of the present application under 35 U.S.C. §103 on a statement that the use of ethanol is considered merely to be a choice among known conventional excipients. Applicant acknowledges that ethanol has previously been used in pharmaceutical compositions. However, the purpose for which ethanol has been included has been either as a solvent or as a preservative against bacterial contamination. There was, however, no reason to suppose that either of these functions of ethanol would have had any beneficial effects in terms of limiting the degradation of ranitidine in aqueous formulations thereof.

For this reason, there would have been no motivation whatever for one of ordinary skill in the art to include ethanol in an aqueous ranitidine formulation. Ranitidine is very soluble in water and ethanol is quite unnecessary to assist in the dissolution of ranitidine in the formulation. In addition, other and better preservatives are available.

Furthermore, there is a clear disincentive against the use of ethanol in aqueous formulations. Thus, an important use of ranitidine is in the treatment of peptic ulcers and related conditions, and it is well known that alcohol (i.e., ethanol) can aggravate such conditions. In fact, the amount of ethanol required for use according to the present invention is at such a low level that no adverse effects are observed as a result of the presence of ethanol, but fairly clear and beneficial effects on drug stability are evident.

However, the fact that ethanol has a known effect in aggravating one of the main conditions that the compositions according to the invention are intended to treat would be a clear disincentive to including ethanol without knowledge of the beneficial effects on stability. This knowledge is, of course, provided only by the present invention. Thus, there was no motivation whatever for one of ordinary skill in the art to include ethanol in aqueous ranitidine formulations and the beneficial effects obtained by the use of ethanol were most definitely unexpected.

Applicant notes that a claim for priority of United Kingdom Application No. 8629781 was made in the Declaration of the grandparent application Serial No. 07/131,442, and a certified copy of the priority document was filed in the grandparent application. Accordingly, it is most respectfully requested that the Examiner acknowledge the claim for priority and the filing of the priority document in the next Official Action in the present application.

In view of the above comments and of the submission of the Declaration of Dr. Hempenstall, favorable reconsideration and allowance of all claims now present in the application are believed to be in order and are most respectfully requested.

Respectfully submitted,

Richard E. Fichter

Richard E. Fichter
Registration No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
Telephone: (703) 683-0500

REF/er

Date: May 10, 1991

LO494804.A2

#11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
David R Long

Serial No. 07/494804 Group Art Unit: 125

Filed: 14 March 1990 Examiner Gardner

For: PHARMACEUTICAL COMPOSITION

DECLARATION

I, JOHN HEMPENSTALL, A British subject and a resident of 49 Seymour Road, St. Albans, Hertfordshire, England, do hereby declare as follows:-

1. I am a Research Leader in the Pharmacy Division of Glaxo Group Research Limited, a subsidiary of Glaxo Group Limited.

2. I obtained the degree of Bachelor of Science (Pharmacy), with honours, in 1977 at the University of Aston in Birmingham and a Doctorate in Pharmaceutical Sciences at the same University in 1982. I am a member of the Royal Pharmaceutical Society of Great Britain. I joined the Pharmacy Division of Glaxo Group Research in 1982 and was appointed to my present position in 1988.

3. Ranitidine is a highly effective therapeutic agent in man for the treatment of gastric and duodenal ulcers. It is administered to the patient in several forms including parenteral and oral administration.

4. In the development of any pharmaceutical presentation it is necessary to ensure that the drug substance is stable within the formulation for as long a time period as is practical, so that the

-1-

patient is receiving the correct dosage and also that he or she is not receiving significant amounts of breakdown products arising from the degradation of the drug substance in the formulation. This latter point is particularly important since it is not always possible to fully identify all the breakdown products that can occur and consequently one cannot determine the chronic toxicity of all the various compounds arising from the breakdown of the drug substance.

5. In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and surprising enhancement in the stability of the ranitidine is achieved by the addition of ethanol to the formulation. The advantageous effect resulting from the addition of ethanol to an aqueous based ranitidine formulation can readily be determined by comparing the stability of the ranitidine in a formulation according to the present invention and the same formulation but without the added ethanol.

6. In US Serial No. 07/494804 there is provided an example of a typical ranitidine oral liquid formulation according to the invention.

Stability studies were carried out comparing this formulation with a formulation that was identical except that it did not contain ethanol. Samples of each formulation were stored at 30^0C, 37^0C and 45^0C for approximately 3 years and the ranitidine content measured by high performance liquid chromatography (h.p.l.c.) against a standard, which was the corresponding formulations stored at 4^0C. At each temperature 2 samples of the formulation without ethanol, identified as Batches 1 and 2 were analysed along with 3 samples of the formulation with ethanol identified as Batches 3, 4 and 5. The specific formulations used in the study were as follows:-

Ranitidine oral liquid formulation (150mg/10ml expressed as free base)

	With Ethanol % w/v	Without Ethanol % w/v
Ranitidine hydrochloride	1.68	1.68
Ethanol	7.5	
Potassium dihydrogen orthophosphate	0095	0.095
Disodium hydrogen orthophosphate anhydrous	0.350	0.350
Hydroxypropylmethylcellulose	qs	qs
Preservative	qs	qs
Sweetening agents	qs	qs
Flavour	qs	qs
Purified water BP to	100ml	100ml

The acceptable shelf life for an aqueous formulation containing ranitidine hydrochloride is considered to be the time at which no more than 5% of the ranitidine present in the formulation has degraded. Accordingly, the figure determined from the stability studies was the time (in months) for 5% ranitidine loss calculated as the lower 95% confidence limit. The results are as follows:

	Without Ethanol		With 7.5% Ethanol		
Temperature	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
30^0C	12.5	13.6	19.5	17.0	20.8
37^0C	5.4	4.7	7.8	7.1	7.5
45^0C	1.8	2.3	2.9	2.9	2.8

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Thus the formulation with ethanol has an average shelf life at 30^0C of 19 months compared with 13 months when ethanol is excluded from the formulation. This is a highly significant and valuable improvement.

The stability of oral liquid formulations as described above except containing varying amounts of ethanol was also studied at 37^0C and 45^0C. The clear advantageous effects of the presence of ethanol can be seen from the following table which gives the time (in months) for 5% ranitidine loss (calculated as the lower 95% confidence limit).

Temperature	% Ethanol				
	0	2.5	5.0	7.5	10.0
37^0C	5.9	7.2	7.6	7.7	6.4
45^0C	2.1	2.4	2.4	2.6	2.7

7. The above results clearly show that ethanol has a beneficial effect upon the stability of ranitidine in aqueous based formulations and furthermore I am not aware of any teaching in the art that would lead me to expect such an effect.

8. I declare further that all statements made herein to my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that each wilful false statement may jeopardise the validity of the application or any patent issuing thereon.

JOHN HEMPENSTALL

Date: 12th April 1991

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/494,864	03/14/90	LONG	

EXAMINER
GARDNER, D
ART UNIT | PAPER NUMBER
17/E
XCP
6/3/91

RICHARD E. FICHTER
BACON & THOMAS
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314

DATE MAILED: 06/03/91

NOTICE OF ALLOWABILITY

PART I.

1. [X] This communication is responsive to papers filed on May 10, 1991
2. [X] All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. [X] The allowed claims are 1-3,5-7,12-17; now 1-3,4-6,7,11,12,8,9,10
4. [ ] The drawings filed on _____ are acceptable.
5. [X] Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [X] been filed in parent application Serial No. 07/131442 filed on 12-11-87
6. [X] Note the attached Examiner's Amendment.
7. [ ] Note the attached Examiner Interview Summary Record, PTOL-413.
8. [ ] Note the attached Examiner's Statement of Reasons for Allowance.
9. [ ] Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. [ ] Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. [ ] Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. [ ] APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. [ ] Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. [ ] The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. [ ] Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. [ ] Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:
- [X] Examiner's Amendment
- [ ] Examiner Interview Summary Record, PTOL-413
- [ ] Reasons for Allowance
- [ ] Notice of References Cited, PTO-892
- [ ] Information Disclosure Citation, PTO-1449
- [ ] Notice of Informal Application, PTO-152
- [ ] Notice re Patent Drawings, PTO-948
- [ ] Listing of Bonded Draftsmen
- [ ] Other

Frederick E. Waddell
Supervisory Patent Examiner
Group 120

PTOL-37 (REV. 11-88)

90

USCOMM-DC 88-3815

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Claim 1 is amended as follows:

1. (Twice amended) A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5-7.5.

Any inquiry concerning this communication should be directed to Diane Gardner at telephone number (703) 308-4610.

Frederick E. Waddell
Supervisory Patent Examiner
Group 120

Gardner:dlg
May 30, 1991

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

RICHARD E. FICHTER
BACON & THOMAS
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

APPLN. NO.	DATE MAILED	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	PAPER NUMBER	ISSUE DATE
07/494,804	03/14/90	012	GARDNER, D	125	06/03/91

ATTORNEY DOCKET NO.	FIRST NAMED APPLICANT
LONG.	DAVID R.

AQUEOUS RANITIDINE COMPOSITIONS STABILIZED WITH ETHANOL (AS AMENDED)

TITLE MOD.	CLASS/SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	514-471.000	Q09	UTILITY	NO	$1050.00	09/03/91

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the Status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or

B. If the Status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by a charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees.

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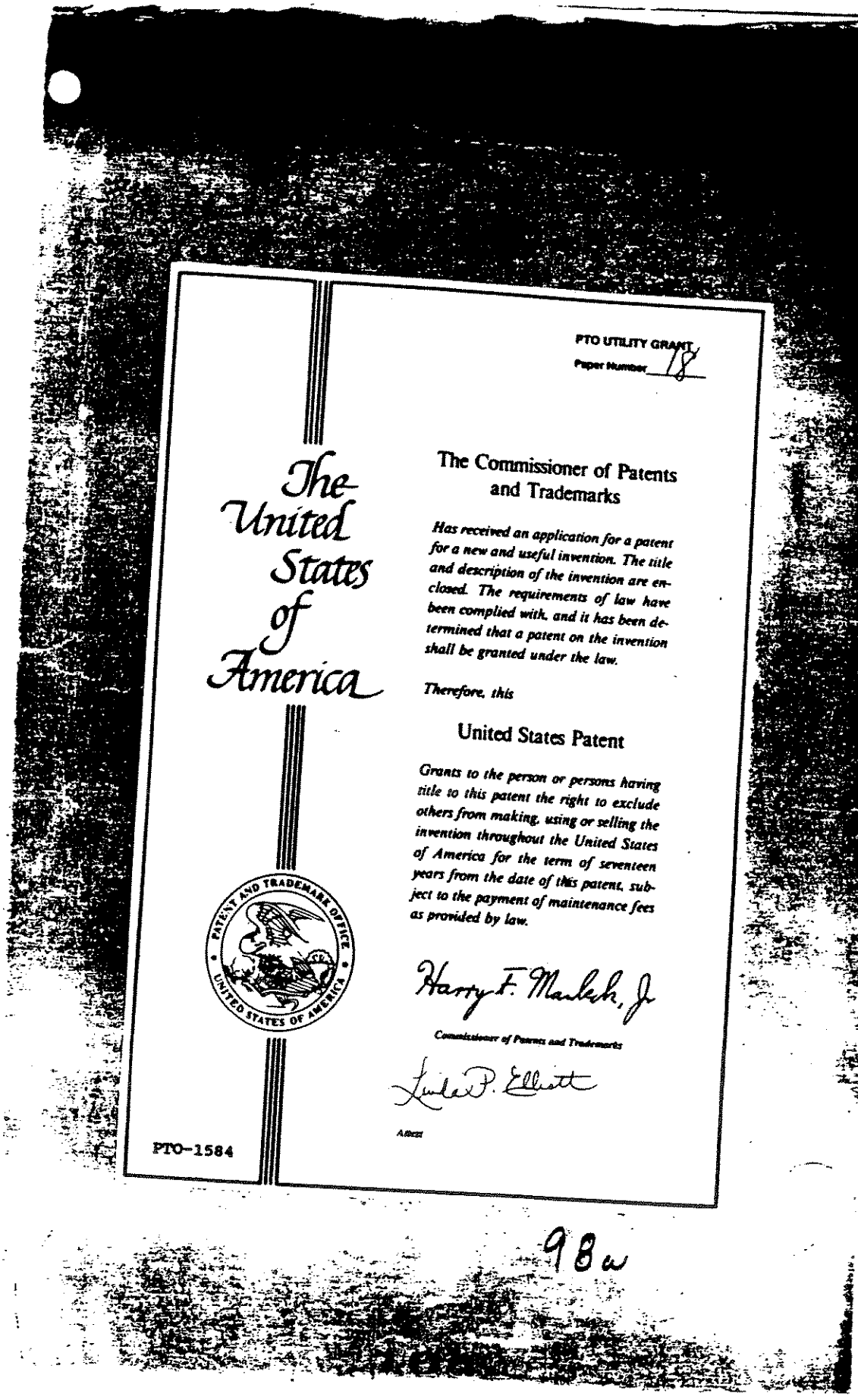
PTOL-85 (REV 12-88)(OMB Clearance is pending) PATENT AND TRADEMARK OFFICE COPY



PTO UTILITY GRANT
Paper Number 18

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Harry F. Manbeck, Jr.

Commissioner of Patents and Trademarks

Linda P. Elliott

Attest

PTO-1584

98w

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Serial No.: 07/344,620

Applicant: David R. LONG

Group Art Unit: 125

Filing Date: April 28, 1989

Examiner: Friedman

For: PHARMACEUTICAL COMPOSITIONS

PETITION FOR EXTENSION OF TIME

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

Applicant requests that the time for taking action in this case be extended pursuant to 37 CFR 1.136 (a) for:

☒ one month ☐ three months
☐ two months ☐ four months

The fee set in 37 CFR 1.17 for the extension of time is $ 62 .

☒ Fee enclosed. Please charge any additional fee required for this extension of time to Deposit Account No. 02-0200 . A duplicate copy of this paper is enclosed.

☐ Charge fee to Deposit Account No. _____. A duplicate copy of this paper is enclosed.

☐ Applicant is a small entity entitled to pay reduced fees in this application. A verified small entity statement:

☐ has been filed ☐ is enclosed

Also enclosed is a:

☐ Response ☐ Notice of Appeal ☐ Appeal Brief

☒ Rule 1.62 File Wrapper Continuation Application w/$370

Respectfully submitted,

Richard E. Fichter
Registration No. 26,382

BACON & THOMAS
625 Slaters Lane - Fourth Floor
Alexandria, Virginia 22314
(703) 683-0500

March 14, 1990

071 49480+

A. PTO form(s) 892 and/or 1449

- [x] 1. At least one form is in file.
- [x] 2. U.S. entries include patent number, name of reference, month and year
- [x] 3. Foreign entries include publication number, country, month and year
- [x] 4. Class and subclass boxes have classification entered or lined through

B. Amendments

- [x] 1. Amendments have been entered as instructed
- [ ] 2. Claims have been renumbered as indicated by Examiner

C. Abstract

- [x] 1. Abstract is on separate page
- [x] 2. Serial number is present and correct
- [x] 3. Contains 250 words or less
- [x] 4. No more than 1 paragraph

D. Specification

- [x] 1. Continuing data is mentioned in the first paragraph or an insert before the first paragraph
- [x] 2. Continuing data has been updated
- [x] 3. Continuing data agrees with face of file
- [x] 4. There are no unclear words because of holes at top of any page
- [x] 5. Pencil notations erased
- [x] 6. Foreign priority on face of file agrees with Oath/Declaration
- [N/A] 7. Certified copy of foreign priority document present
- [x] 8. Examiner has acknowledged foriegn priority
- [N/A] 9. On reissues, original grant is enclosed

E. Claims

- [x] 1. All claims are either renumbered or cancelled
- [x] 2. Total number in "Index of Claims" corresponds to "Claims Allowed"
- [x] 3. Total number in "Index of Claims" corresponds with PTOL 37 and 85

F. Issue Classification Slip

- [x] 1. Issue classification slip affixed to Staple Area
- [x] 2. Serial number present and correct
- [x] 3. Applicant's name present and correct
- [x] 4. Signed by Primary Examiner
- [x] 5. Assistant Examiner box is either signed or lined through

G. Right Outside File Jacket

- [x] 1. "Searched" box is completed
- [x] 2. "Intereference Searched" box is completed
- [ ] 3. An issue fee authorization stamp is present

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Signature Irene Pittman Date 6/24/91

PART B - ISSUE FEE TRANSMITTAL 1050-142-B

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advanced orders and notification of maintenance fees will be mailed to addressee indicated in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. See reverse for Certificate of Mailing.

RECEIVED AUG 29 1991 PAT. & TRADEMARK OFF.

1 CORRESPONDENCE ADDRESS

RICHARD E. FICHTER
BACON & THOMAS
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314

2 INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change)

INVENTOR'S NAME
Street Address
City, State and ZIP Code
CO-INVENTOR'S NAME
Street Address
City, State and ZIP Code
☐ Check if additional changes are on reverse side

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
07/494,804	03/14/90	012	GARDNER, D	125	06/03/91

First Named Applicant: LONG, DAVID R.

TITLE OF INVENTION: AQUEOUS RANITIDINE COMPOSITIONS STABILIZED WITH ETHANOL (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
514-471.000	514/909		UTILITY	NO	$1050.00	09/03/91

3. Further correspondence to be mailed to the following:
Richard E. Fichter
BACON & THOMAS
625 Slaters Lane - 4th Floor
Alexandria, Virginia 22314

4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.
1 BACON & THOMAS
2
3

080 BF 09/04/91 07494804

DO NOT USE THIS SPACE
1 142 1,050.00 CK

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)
(1) NAME OF ASSIGNEE: GLAXO GROUP LIMITED 03
(2) ADDRESS: (City & State or Country) London, England GB2
(3) STATE OF INCORPORATION, IF ASSIGNEE IS A CORPORATION

A. ☐ This application is NOT assigned.
☒ Assignment previously submitted to the Patent and Trademark Office.
☐ Assignment is being submitted under separate cover. Assignments should be directed to Box ASSIGNMENTS.

PLEASE NOTE: Unless an assignee is identified in Block 5, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

6a. The following fees are enclosed:
☒ Issue Fee ☐ Advanced Order - # of Copies

6b. The following fees should be charged to: (Minimum of 10)
DEPOSIT ACCOUNT NUMBER 02-0200
(Enclose Part C)
☐ Issue Fee ☐ Advanced Order - # of Copies
☒ Any Deficiencies in Enclosed Fees (Minimum of 10)

The COMMISSIONER OF PATENTS AND TRADEMARKS is requested to apply the Issue Fee to the application identified above.

(Signature of party in interest of record) Richard E. Fichter, Reg. No. 26,382 (Date) 8-29-91

NOTE: The Issue Fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office.

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TRANSMIT THIS FORM WITH FEE-CERTIFICATE OF MAILING ON REVERSE

PTOL-85B (REV 12-88)(OMB Clearance in pending)

US-CL-CURRENT: 514/212, 319, 323, 324, 397; 540/603; 546/200; 548/336

US PAT NO: 4,913,080 LS: 6 of 26
TITLE: Imidazolilyl containing ketone derivatives

ABSTRACT:
The present invention provices ketones of the general formula (I): ##STR1## and physiologically acceptable salts and solvates thereof, w hydrogen atom or a C.sub.1-6 alkyl, C.sub.3-7 cycloalkyl, C.sub.3-6 alkenyl, phenyl or phenyl C.sub.1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C.sub.1-6 alkyl group; and an aromatic or heteroaromatic group as defined in the specification.
The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT.sub.3 receptors and are useful, for exaaple, in the treatment of psychotic disorders, anxiety and nausea and vomiting.
US-CL-CURRENT: 514/300, 397; 540/524; 546/113, 168; 548/336, 342

US PAT NO: 4,850,636 LS: 7 of 26
TITLE: Film coated tablet of **ranitidine** HCl

ABSTRACT:
This invention relates to an improved polymeric film coating for a **ranitidine** Hydrocholride (HCl) tablet in which the plasticizer triacetin had been added to the polymeric fila coating medium. A tablet of this invention has been found to have great **stability** than a tablet coating with a polymeric film which does not contain triacetin.
US-CL-CURRENT: 4rage molecular
weight hydroxypropylmethylcellulose, a high number average molecular weight hydroxypropylmethylcellulose, and a beneficial drug.
US-CL-CURRENT: 424/488, 451, 464, 470

US PAT NO: 4,859,662 LS: 9 of 26
TITLE: Tetrahydro-imidazolylmethylcarbazolones and analogs thereof for treating 5-HT function distrbances

ABSTRACT:
The invention relates to compounds of the general formula (I): ##STR1## wherein Im represents an imidazolyl group of the formula: ##STR2## and the various substituents are defined hereinbelow. The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT.sub.3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.
US-CL-CURRENT: 514/212, 323, 397; 540/603; 546/200; 548/336

US PAT NO: 4,851,228 [IMAGE AVAILABLE] LS: 10 of 26
TITLE: Multiparticulate controlled porosity osmotic

ABSTRACT:
The instant invention is directed to a multiparticulate osmotic pump, for the controlled release of a pharmaceutically active agent to an environment of use, said pump comprising:
(I) a carrier medium which does not maintain its liter solubility in the external fluid with an osmotically effective solute that is soluble in the fluid, which exhibit an osmotic pressure gradient across the wall against the external fluid surrounded by
(B) a rate controlling water insoluble wall, having a fluid permeability of 1.76.times.10.sup.-12 to 2.76.times.10.sup.-4 cm.sup.3 sec/g and a reflection coefficient of less than 0.2, prepared from:
(i) a polymer permeable to water but impermeable to solute and
(ii) 0.1 to 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout said wall.

US-CL-CURRENT: 424/451, 464, 470, 497, 498; 428/402.2, 407

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